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ORIGINAL ARTICLE

Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer

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ABSTRACT

BACKGROUND

Primary debulking surgery before initiation of chemotherapy has been the standard of care for patients with advanced ovarian cancer.

METHODS

We randomly assigned patients with stage IIIC or IV epithelial ovarian carcinoma, fallopian-tube carcinoma, or primary peritoneal carcinoma to primary debulking surgery followed by platinum-based chemotherapy or to neoadjuvant platinum-based chemotherapy followed by debulking surgery (so-called interval debulking surgery).

RESULTS

Of the 670 patients randomly assigned to a study treatment, 632 (94.3%) were eligible and started the treatment. The majority of these patients had extensive stage IIIC or IV disease at primary debulking surgery (metastatic lesions that were larger than 5 cm in diameter in 74.5% of patients and larger than 10 cm in 61.6%). The largest residual tumor was 1 cm or less in diameter in 41.6% of patients after primary debulking and in 80.6% of patients after interval debulking. Postoperative rates of adverse effects and mortality tended to be higher after primary debulking than after interval debulking. The hazard ratio for death (intention-to-treat analysis) in the group assigned to neoadjuvant chemotherapy followed by interval debulking, as compared with the group assigned to primary debulking surgery followed by chemotherapy, was 0.98 (90% confidence interval [CI], 0.84 to 1.13; $P=0.01$ for non-inferiority), and the hazard ratio for progressive disease was 1.01 (90% CI, 0.89 to 1.15). Complete resection of all macroscopic disease (at primary or interval surgery) was the strongest independent variable in predicting overall survival.

CONCLUSIONS

Neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV ovarian carcinoma in this study. Complete resection of all macroscopic disease, whether performed as primary treatment or after neoadjuvant chemotherapy, remains the objective whenever cytoreductive surgery is performed. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00003636.)

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IN MOST WOMEN WITH OVARIAN CARCINOMA, the disease is not diagnosed until it is at an advanced stage. Primary cytoreductive surgery is considered the standard of care for advanced ovarian carcinoma.¹⁻⁴ However, data from prospective, randomized, controlled trials assessing the role of primary surgery in the treatment of such cases are lacking. Interval debulking surgery has not been viewed as beneficial in women with residual tumor that exceeds 1 cm in diameter after primary debulking surgery performed with the objective of maximal surgical effort by a gynecologic oncologist.⁵⁻⁷ As an alternative to primary debulking surgery followed by chemotherapy, some authors have investigated the use of neoadjuvant chemotherapy before cytoreductive surgery. However, results of a meta-analysis involving 835 patients suggested that neoadjuvant chemotherapy, as compared with primary debulking surgery, was associated with a worse outcome.⁸

We report on a randomized trial in which we compared primary debulking surgery followed by platinum-based chemotherapy and platinum-based neoadjuvant chemotherapy followed by interval debulking surgery and additional platinum-based chemotherapy in women with advanced ovarian carcinoma.

METHODS

PATIENTS

Eligible patients had biopsy-proven stage IIIC or IV invasive epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian-tube carcinoma. If a biopsy specimen was not available, a fine-needle aspirate showing an adenocarcinoma was acceptable under the following conditions: the presence of a pelvic (ovarian) mass; the presence of metastases outside the pelvis measuring at least 2 cm in diameter (as noted during diagnostic laparoscopy or laparotomy or on computed tomography [CT]); regional lymph-node metastasis or proof of stage IV disease; and a ratio of cancer antigen 125 (CA-125, measured in kilounits per liter) to carcinoembryonic antigen (CEA, measured in nanograms per milliliter) that was greater than 25. The CA-125:CEA ratio has been shown to be useful for ruling out primary gastrointestinal tumors that have metastasized to the peritoneum, the ovaries, or both.⁹ If the serum CA-125:CEA ratio was 25 or lower, results of a barium enema (or colonoscopy), gastroscopy (or radio-

logic examination of the stomach), and mammography (performed within 6 weeks before randomization) had to be negative for the presence of a primary tumor. Additional prerandomization requirements included a World Health Organization (WHO) performance status of 0 (asymptomatic) to 2 (symptomatic, in bed for less than half the day)¹⁰ and the absence of serious disabling diseases that would contraindicate primary cytoreductive surgery or platinum-based chemotherapy. (Other inclusion criteria are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Before receiving treatment, all patients provided written informed consent. Because of an allegation of ethical irregularities at one of the centers with regard to another European Organization for Research and Treatment of Cancer (EORTC) protocol, all the patients from that center who were enrolled in this study were excluded from the analysis.

STUDY DESIGN

Patients had to start the assigned treatment within 3 weeks after the initial biopsy or fine-needle aspiration. The biopsy could be image-guided or carried out during laparoscopy or laparotomy. Patients who underwent laparotomy or laparoscopy were not allowed to undergo any procedures other than the diagnostic biopsies. Randomization was done centrally at the EORTC headquarters after stratification, with the use of a minimization technique to stratify for institution, method of biopsy (image-guided, laparoscopy, laparotomy, or fine-needle aspiration), tumor stage (IIIC or IV), and largest preoperative tumor size (excluding ovaries) (≤ 5 cm, >5 to 10 cm, >10 to 20 cm, or >20 cm).

Patients were randomly assigned either to primary debulking surgery followed by at least six courses of platinum-based chemotherapy or to three courses of neoadjuvant platinum-based chemotherapy followed by interval debulking surgery in all patients with a response or stable disease, followed in turn by at least three courses of platinum-based chemotherapy. In patients randomly assigned to primary debulking whose surgery was completed without optimal cytoreduction, interval debulking surgery was permitted if stable disease or a response was documented, and these patients were included in the primary-surgery group for analyses. After the results of the Gynecologic Oncology Group trial (GOG-152)

(NCT00002568) were published,⁶ interval debulking surgery was no longer recommended for patients in whom optimal cytoreduction was not achieved despite a maximal effort at primary debulking surgery. Data on the timing of interval debulking surgery and chemotherapy, chemotherapy regimens, and assessments are provided in the Supplementary Appendix. All surgical procedures had to be performed by qualified gynecologic oncologists who were appointed by the individual institutions before the start of the study, and all patients were evaluated for eligibility before randomization, with no additional selection criteria (including resectability) imposed by the surgeon. No CT or laparoscopic scoring systems were used in the selection of the patients.

The study was designed and the manuscript written by the first author in cooperation with the other authors. Data were gathered at the EORTC headquarters and analyzed in cooperation with the authors by the EORTC statistician, who vouches for the accuracy of the data and the analyses. The decision to submit the manuscript for publication was made by the authors in agreement with the EORTC–Gynaecological Cancer Group (EORTC-GCG) and the National Cancer Institute of Canada (NCIC) Clinical Trials Group. The study was approved by the EORTC Protocol Review Committee, the NCIC Clinical Trials Group Clinical Trials Committee, and the institutional review board of each participating institution. An independent data and safety monitoring committee was appointed to monitor the recruitment rate, the potential toxicity of the treatments, and the optimal percentage of debulking. The drugs administered for adjuvant chemotherapy were purchased by the individual institutions. The study was conducted in accordance with the protocol as amended. (The trial protocol is available at NEJM.org.)

EVALUATION AND FOLLOW-UP

Patients filled out two EORTC quality-of-life questionnaires at five time points during the study: EORTC QLQ-C30 (http://groups.eortc.be/qol/questionnaires_qlqc30.htm) and QLQ-Ov28 (http://groups.eortc.be/qol/downloads/modules/specimen_20qlq_ov28.pdf).

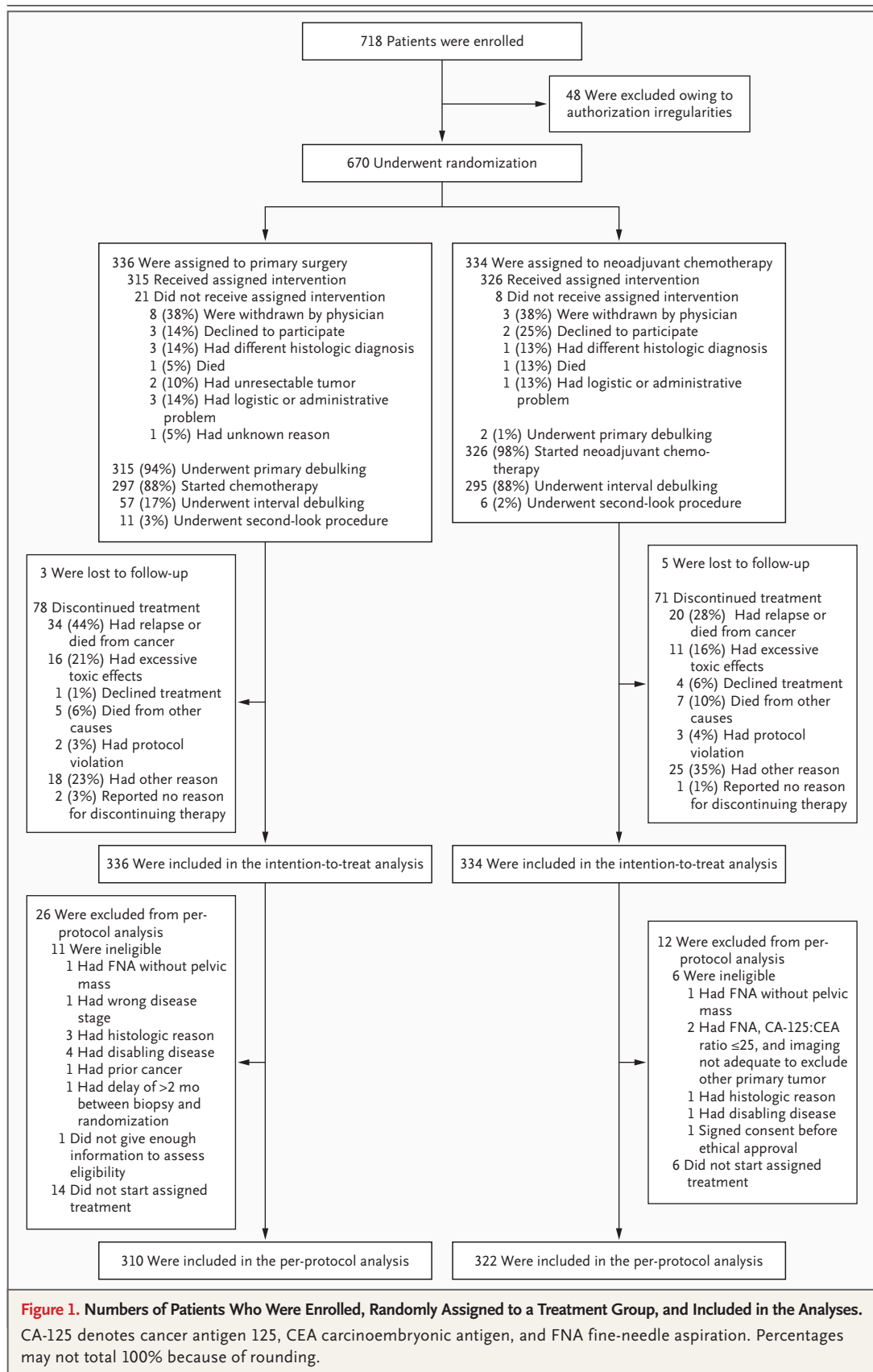
Tumor response during chemotherapy was evaluated according to the WHO criteria.¹¹ In addition, progression of disease after first-line chemotherapy was defined by an increase by a

factor of at least 2 in the nadir serum CA-125 level according to the Gynaecologic Cancer Inter-group criteria.¹²

STATISTICAL ANALYSIS

The primary end point of the study was overall survival. The group undergoing primary debulking surgery was considered to be the standard-treatment group. On the basis of the earlier experience of the EORTC institutions, about 50% of patients with stage IIIC or IV ovarian carcinoma who underwent debulking surgery had a residual tumor size of 1 cm or less and had a median survival of 36 months.¹³ On the basis of a previous EORTC trial of interval debulking surgery, median survival among the patients with suboptimal primary debulking who underwent interval surgery was expected to be 26 months.⁵ Thus, the median survival of the whole group of patients randomly assigned to primary surgery was expected to be 31 months. With an accrual time of 4 years and a minimum follow-up period of 3 years, 498 events (704 patients) were required to show noninferiority of interval debulking surgery as compared with primary surgery, with a one-sided type I error rate of 0.05 and a power of 80%. A hazard ratio of less than 1.25 was considered to indicate noninferiority. Secondary end points were adverse effects, quality of life, and progression-free survival. No interim analyses were planned or conducted.

The analysis was planned to be performed according to the intention-to-treat principle: all randomly assigned patients were included in the primary analysis, regardless of whether they were eligible and whether they could be evaluated. A secondary analysis was based on the treatment actually received. For definitions of overall and progression-free survival, see the Supplementary Appendix. Overall and progression-free survival rates were estimated by means of the Kaplan–Meier method, and overall survival rates in the two groups were compared by means of the log-rank test, with a noninferiority ratio of 0.8. Multivariate time-to-event analysis was performed with the use of a Cox proportional-hazards model and univariate screening followed by a stepwise variable-selection procedure.¹⁴ Adverse events were reported in contingency tables with the use of the National Cancer Institute Common Toxicity Criteria, version 2.0 (http://ctep.cancer.gov/protocoldevelopment/electronic_



applications/docs/ctcv20_4-30-992.pdf); comparisons between treatment groups were made with the use of the log-rank test for trend. Adverse effects were regarded as postoperative if they occurred within 28 days after surgery. The largest metastases before randomization were measured during diagnostic laparoscopy or laparotomy, and if neither of these tests was done, their size was determined on the basis of CT findings.

RESULTS

CHARACTERISTICS OF THE PATIENTS AND TREATMENT RECEIVED

From September 1998 through December 2006, a total of 718 patients were enrolled in the study; 48 patients were excluded because of potential authorization irregularities at one institution (Fig. 1). The remaining 670 patients were randomly assigned to treatment at 59 institutions (median accrual per institution, 5 patients; range, 1 to 125) (Fig. 1).

The results of the study were similar whether the 48 patients from the one center with possible irregularities were included or excluded. The requisite number of events was reached in August 2008 (median follow-up, 4.7 years).

The baseline characteristics of the patients were well balanced between the two treatment groups (Table 1). Details regarding residual tumor size, size of largest residual tumor per country, type of surgery, type of chemotherapy and number of courses, and time to initiation (or reinitiation) of chemotherapy are summarized in Table 1 in the Supplementary Appendix. The residual tumor size was 1 cm or smaller after primary debulking surgery in 41.6% of patients and after interval debulking surgery in 80.6% of patients.

After debulking surgery, the primary diagnosis changed in 11 patients (3.3%) assigned to primary debulking surgery and in 7 patients (2.1%) assigned to neoadjuvant chemotherapy followed by interval debulking surgery (5 carcinosarcomas, 4 endometrial carcinomas, 2 gastrointestinal tumors, 2 borderline tumors of the ovary, 1 cervical adenocarcinoma, 1 stage IC ovarian carcinoma, 1 teratoma, 1 rhabdomyosarcoma, and 1 pseudomyxoma).

The diaphragm, abdominal peritoneum, and pelvis (pouch of Douglas, uterus, bladder, rectum, and sigmoid) were the most frequent sites of residual tumor after both primary debulking and

interval debulking surgery. Details on the size and site of the metastases before and after primary and interval debulking surgery, as well as the debulking rates after interval debulking in patients in the primary-surgery group, are summarized in the Supplementary Appendix. Within each country, there was a strong correlation between the rates of optimal debulking at primary debulking surgery and at interval debulking surgery ($r=0.92$).

PERIOPERATIVE AND POSTOPERATIVE MORBIDITY, MORTALITY, AND QUALITY OF LIFE

Perioperative and postoperative morbidity and mortality are summarized in Table 1 in the Supplementary Appendix. Postoperative death (defined as death <28 days after surgery) occurred in 2.5% of patients in the primary-surgery group and in 0.7% of patients in the neoadjuvant-chemotherapy group. Grade 3 or 4 hemorrhage occurred in 7.4% of patients after primary debulking and in 4.1% after interval debulking, infection in 8.1% and 1.7%, respectively, and venous complications in 2.6% and 0%, respectively. Analyses comparing the perioperative and postoperative characteristics of the two groups were not performed because the groups were unequal — that is, not all patients who were randomly assigned to primary debulking underwent primary debulking surgery, and not all patients assigned to neoadjuvant chemotherapy underwent interval debulking surgery.

At none of the assessment times were the differences in the QLQ-C30 global health scores significant. The overall test for a treatment effect on global health was also not significant.

OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL

Overall survival was similar in the two groups in the intention-to-treat analyses (Fig. 2A), as was progression-free survival (Fig. 1 in the Supplementary Appendix). The median overall survival was 29 months in the primary-surgery group and 30 months in the neoadjuvant-chemotherapy group, and the median progression-free survival in both groups was 12 months. On the basis of the intention-to-treat analysis, the hazard ratio for death in the group assigned to neoadjuvant chemotherapy followed by interval debulking, as compared with the group assigned to primary debulking, was 0.98 (90% confidence interval [CI], 0.84 to 1.13; $P=0.01$ for noninferiority), and the hazard

ratio for progressive disease was 1.01 (90% CI, 0.89 to 1.15). The analysis according to treatment actually received (per-protocol analysis) showed similar results for overall survival (hazard ratio for death, 1.00; 90% CI, 0.85 to 1.16; $P=0.01$ for noninferiority) (Fig. 2 in the Supplementary Appendix). Figure 2B shows overall survival according to treatment group and amount of residual

tumor (per-protocol analysis). Overall survival in the group of patients who underwent primary debulking surgery initially and then interval debulking surgery was similar to that in the group of patients who were randomly assigned to neoadjuvant chemotherapy (Fig. 3 in the Supplementary Appendix).

In a post hoc attempt to identify subgroups

Table 1. Baseline Characteristics of the Patients.

Characteristic	Primary Debulking Surgery (N=336)	Neoadjuvant Chemotherapy (N=334)
Age — yr		
Median	62	63
Range	25–86	33–81
WHO performance status — no. (%) [*]		
0	153 (45.5)	147 (44.0)
1	141 (42.0)	143 (42.8)
2	40 (11.9)	44 (13.2)
Missing data	2 (0.6)	0
Histologic type — no. (%)		
Serous	220 (65.5)	194 (58.1)
Mucinous	8 (2.4)	11 (3.3)
Clear-cell	6 (1.8)	4 (1.2)
Endometrioid	11 (3.3)	5 (1.5)
Undifferentiated	69 (20.5)	90 (26.9)
Mixed	3 (0.9)	0
Other or unknown	19 (5.7)	30 (9.0)
Histologic grade — no. (%)		
Well differentiated	14 (4.2)	10 (3.0)
Moderately differentiated	57 (17.0)	41 (12.3)
Poorly differentiated	145 (43.2)	130 (38.9)
Unknown	120 (35.7)	153 (45.8)
Stage — no. (%)		
IIIC	257 (76.5)	253 (75.7)
IV	77 (22.9)	81 (24.3)
Other	2 (0.6)	0
Malignant pleural effusion — no. (%)		
No	285 (84.8)	272 (81.4)
Yes	51 (15.2)	62 (18.6)
Method of biopsy — no. (%)		
Laparotomy	12 (3.6)	12 (3.6)
Laparoscopy	104 (31.0)	116 (34.7)
Image guidance	76 (22.6)	53 (15.9)
Fine-needle aspiration	142 (42.3)	153 (45.8)
Missing data	2 (0.6)	0

Table 1. (Continued.)

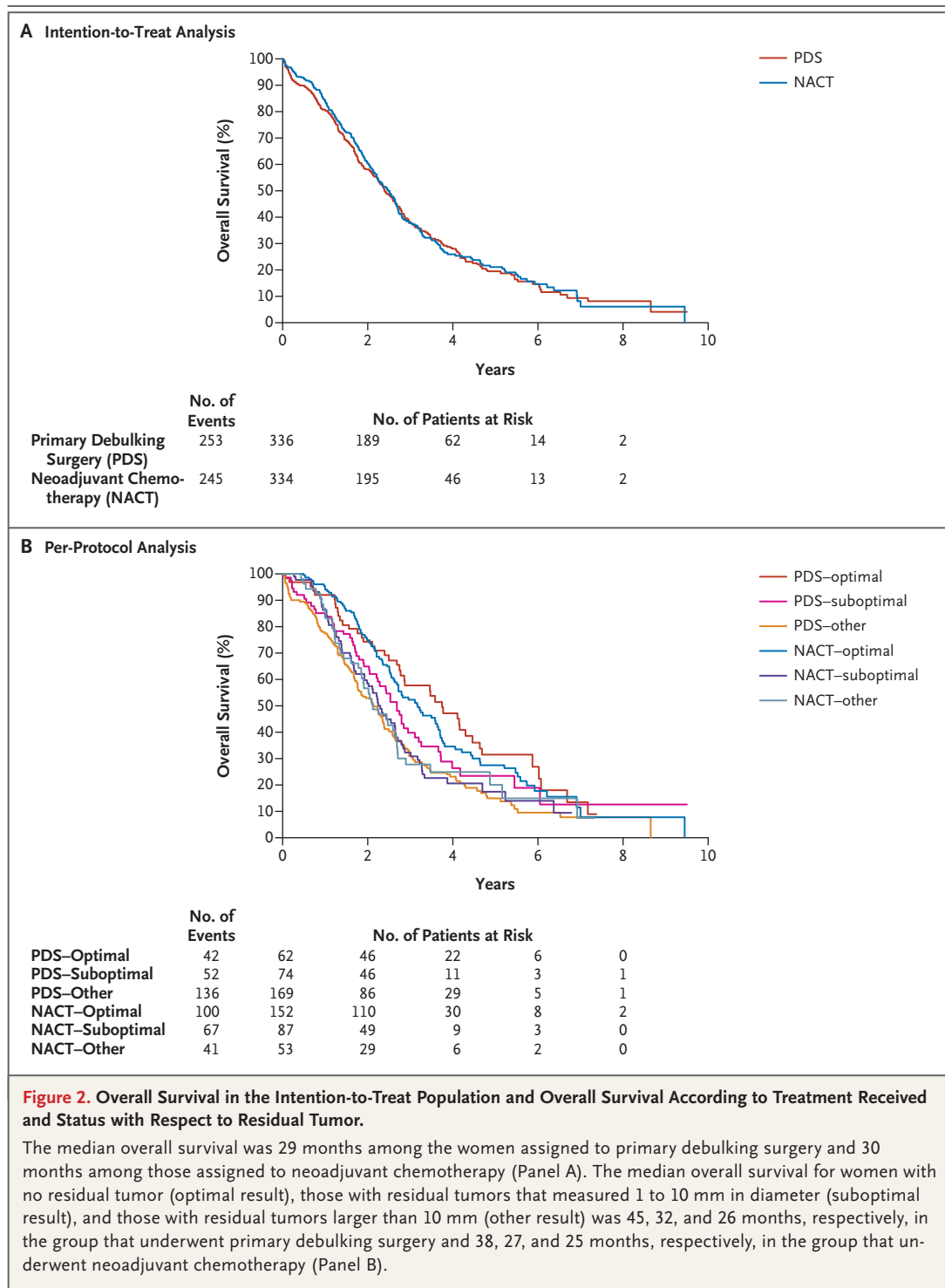
Characteristic	Primary Debulking Surgery (N=336)	Neoadjuvant Chemotherapy (N=334)
Primary tumor — no. (%)		
Epithelial ovarian	293 (87.2)	283 (84.7)
Peritoneal	22 (6.5)	26 (7.8)
Fallopian tube	0	4 (1.2)
Adenocarcinoma	17 (5.1)	20 (6.0)
Missing data	4 (1.2)	1 (0.3)
Serum CA-125 at entry (U/ml)		
Median	1130	1180
Range	16.0–27,185	15.0–41,456
Serum CA-125 >30 U/ml — no. (%)	330 (98.2)	330 (98.8)
Largest metastatic tumor at randomization — no. (%)		
0 cm	2 (0.6)	1 (0.3)
>0–2 cm	2 (0.6)	9 (2.7)
>2–5 cm	90 (26.8)	85 (25.4)
>5–10 cm	90 (26.8)	88 (26.3)
>10–20 cm	105 (31.3)	113 (33.8)
>20 cm	26 (7.7)	24 (7.2)
Missing data	21 (6.3)	14 (4.2)
Size of metastases at the time of surgery — no. (%)†		
No metastasis	1/310 (0.3)	14/322 (4.3)
>0–1 cm	2/310 (0.6)	36/322 (11.2)
>1–2 cm	14/310 (4.5)	40/322 (12.4)
>2–5 cm	50/310 (16.1)	74/322 (23.0)
>5–10 cm	40/310 (12.9)	42/322 (13.0)
>10 cm	191/310 (61.6)	78/322 (24.2)
Missing data	12/310 (3.9)	38/322 (11.8)

* WHO denotes World Health Organization.

† The per-protocol population included only eligible patients who actually underwent primary debulking surgery in the primary-surgery group (310 patients) and patients who actually started chemotherapy in the neoadjuvant-chemotherapy group (322).

of patients in which one of the study treatments tended to be associated with better overall survival, we analyzed the hazard plots in relation to age, the International Federation of Gynecology and Obstetrics (FIGO) stage, WHO performance status, histologic type, and presence or absence of pleural fluid (Fig. 4 to 8 in the Supplementary Appendix). In none of the subgroups was there apparent superiority of one of the treatments. When we evaluated the outcome of debulking to 1 cm or less according to country, no significant differences were noted between the treatment

groups (Fig. 9 in the Supplementary Appendix). When the patients who were randomly assigned by the EORTC-GCG (586 patients) were compared with those randomly assigned by the NCIC Clinical Trials Group (84 patients), the median overall survival was similar (28 and 34 months, respectively). This result is noteworthy, since the proportions of patients with no residual tumor after primary debulking surgery and after interval debulking surgery tended to be higher in the subgroup randomly assigned by the EORTC-GCG (20.4% and 50.0%, respectively) than in the sub-



group assigned by the NCIC Clinical Trials Group (11.1% and 40.5%, respectively). Among patients with metastatic tumors that were less than 5 cm in diameter at randomization, overall survival was

slightly longer in the primary-surgery group than in the neoadjuvant-chemotherapy group (hazard ratio, 0.64; 95% CI, 0.45 to 0.93) (Fig. 10 in the Supplementary Appendix).

MULTIVARIATE ANALYSES

Unadjusted and adjusted Cox regression multivariate analyses were performed post hoc, with overall survival as the end point, and included the following variables: largest residual tumor after primary or interval debulking surgery, largest tumor size before randomization, WHO performance status, age, FIGO stage, histologic type, method of biopsy, histologic grade, treatment group, and country (reduced to eight categories by pooling results from the smallest seven countries). The strongest independent predictors of prolonged survival, in descending order, were the absence of residual tumor after surgery ($P<0.001$); stage IIIC disease ($P=0.001$); small tumor size before randomization ($P=0.001$); endometrioid histologic type, followed in descending order by serous, mixed, undifferentiated, mucinous, and clear-cell types ($P=0.005$); and younger age ($P=0.005$). The other variables did not significantly influence overall survival.

DISCUSSION

In this randomized trial, primary debulking surgery followed by chemotherapy was compared with neoadjuvant chemotherapy followed by interval debulking surgery in women with advanced ovarian cancer. We found that survival after neoadjuvant chemotherapy followed by interval debulking surgery was similar to survival with the standard approach of primary surgery followed by chemotherapy.

This trial did not include patients with FIGO stage IIIB or earlier-stage ovarian carcinoma. Rather, all the study participants had extensive stage IIIC or IV disease. Indeed, most patients had obvious stage IIIC or IV disease; at the time of primary debulking surgery, 61.6% had metastatic lesions that were larger than 10 cm in diameter, and 74.5% had lesions larger than 5 cm. This is noteworthy, since it might be the reason for the poor outcomes with respect to median progression-free and overall survival, as compared with the findings in some single-institution series^{13,15-18}; however, the debulking rates and survival rates in our study are similar to those in other multicenter or regional studies that analyzed stage IIIC and IV ovarian carcinomas separately.¹⁹⁻²⁵ Furthermore, the current study showed no trend in favor of primary debulking in countries with high rates of optimal primary

debulking surgery. This finding might be due to the strong correlation between cytoreduction rates at primary debulking surgery and at interval debulking surgery within each country.

In selecting patients for neoadjuvant chemotherapy, it is important to rule out other primary tumors, especially those of gastrointestinal origin. In this study, a CA-125:CEA ratio higher than 25 was used as an eligibility criterion, since this ratio has been shown to be a good tool for ruling out primary gastrointestinal tumors that have metastasized to the peritoneum or ovaries or to both sites.⁹ The value of this ratio was confirmed in the current study, since only two patients proved to have a gastrointestinal cancer at the time of primary or interval debulking surgery.

Complete resection of all macroscopic disease at primary debulking surgery has been shown to be the single most important independent prognostic factor in advanced ovarian carcinoma.^{13,15-18,25,26} In the current study, the importance of this prognostic factor was confirmed by the results of the multivariate analyses and the survival analyses according to the extent of residual tumor after both primary and interval debulking surgery (Fig. 2B). Given our findings and the results of other studies, a potential approach for debulking surgery could be the elimination of all macroscopic residual disease, rather than the elimination of lesions larger than 1 cm in diameter. A potential drawback of neoadjuvant chemotherapy followed by debulking surgery is that the occurrence of fibrosis after chemotherapy may make complete resection of macroscopic disease more difficult.

In conclusion, among patients with advanced (stage IIIC or IV) ovarian, fallopian-tube, or peritoneal ovarian carcinoma, survival after neoadjuvant chemotherapy followed by interval debulking surgery is similar to survival after primary debulking surgery followed by chemotherapy. This result is consistent with the conclusions of a recent meta-analysis of 21 nonrandomized trials.²⁷ The standard of care for women with stage IIIB or earlier-stage epithelial ovarian cancer — a group with a better prognosis than the current study population — remains primary cytoreductive surgery. Only those patients with proven stage IIIC or IV disease should be considered for neoadjuvant chemotherapy.

In the current study, none of the subgroup

analyses showed a significant difference in survival between the two treatment groups. When deciding whether a patient is a candidate for primary debulking surgery, with an acceptable level of morbidity, the clinician may consider taking into account information from the surgical consultation and could assess important predictive factors with respect to residual macroscopic disease after debulking surgery (e.g., presence or absence of coexisting illnesses, age, disease burden, location of metastatic sites, WHO performance status, and tumor stage). Laparoscopy, in addition to axial CT, positron-emission tomography, or both,²⁸ may provide information about the disease burden.²⁹⁻³² Neoadjuvant chemother-

apy is not inferior to primary cytoreductive surgery for patients with stage IIIC or IV ovarian carcinoma. No significant advantages of neoadjuvant therapy or primary debulking surgery were observed with respect to survival, adverse effects, quality of life, or postoperative morbidity or mortality.

The views expressed in this article are those of the authors and do not necessarily reflect the official views of the National Cancer Institute.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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